

REMARKS

Applicants note with thanks the rejoinder of the species requirement for SEQ ID NOS: 1-6. Other restriction requirements remain.

Amendments

At the suggestion of the examiners during the interview, the word “vaccine” has been deleted from claims 22, 29, 35, 36, 37, and 38 to avoid confusion.

Claim 26 has been amended to provide antecedent basis for the word “epitope.”

New claims 113-115 have been added. These claims are thoroughly supported in the application as filed. Claim 113 recites that the compositions comprises a *Listeria monocytogenes* bacterium. This is supported in claim 36 as originally filed. Claim 114 recites that the encoded polypeptide recited in claim 22 comprises a plurality of epitopes. This recitation is supported at paragraph 42 of the application as filed: “Optionally, the polypeptides of the vaccines (or the polypeptides encoded by the polynucleotides of the vaccines) comprise a plurality of MHC Class I-binding epitopes of mesothelin and/or MHC Class II-binding epitopes of mesothelin.” Claim 115 recites that the encoded polypeptide recited in claim 22 comprises the epitopes of SEQ ID NO: 1-6. This recitation is supported at paragraph 46 of the application as filed: “In another embodiment, the mesothelin protein comprises each of the following amino acid sequences: SLLFLLFSL (SEQ ID NO:1); VLPLTVVAEV (SEQ ID NO:2); ELAVALAQK (SEQ ID NO:3); ALQGGGPPY (SEQ ID NO:4); FYPGYLCSL (SEQ ID NO:5); and LYPKARLAF (SEQ ID NO:6).” Thus the new claims and other amendments add no new matter to the application.

The Rejection of Claims 22-24, 26-28 and 111 Under 35 U.S.C. §112, First Paragraph

All examined claims are rejected as not enabled by the specification. The Office Action provides three reasons for doubting the enablement of the claimed methods:

- A) The specification allegedly provides no evidence in any animal tumor models that shows a correlation between the recited vaccines and induction of mesothelin epitope-specific cytotoxic T lymphocytes.
- B) Pancreatic cancer is so malignant that treatment of it is unpredictable.
- C) Even if animal model data existed, their applicability to humans is unpredictable.

Applicants specifically traverse each of these reasons and provide evidence which refutes them. When the evidence is properly weighed and considered, there are no remaining reasons to doubt the enablement of the claimed invention.

A. The specification allegedly provides no evidence in any animal tumor models that shows a correlation between the recited vaccines and induction of mesothelin epitope-specific cytotoxic T lymphocytes

The specification provides data from animal model studies at Example 11 (pages 57-58) and Figure 11. The example describes the vaccination of mice with DNA encoding mesothelin. The DNA was coated onto gold particles and delivered with a gene gun according to standard protocols. After a priming and booster administration, the mice were challenged with WF-3 tumor cells intraperitoneally. The vaccination achieved a high degree of protection as shown in Figure 11.

WF-3 tumor cells high express mesothelin and form ascites when they grow in the peritoneum. Characterization of the WF-3 model is provided in Examples 6-10 of the specification. Example 6 teaches that WF-3 cells form tumors with a papillary configuration, consistent with tumors from the peritoneum or ovaries. Example 7 teaches that WF-3 cells are positive for MHC class I expression. Example 8 establishes the lethal dose and timing of WF-3 in mice. Example 9 teaches that mesothelin is up-regulated in WF-3 relative to pre-WF0, a cell line which was generated by a method similar to that used to generate WF-3, but without transformation by c-Ha-ras. Up-regulation of mesothelin in WF-3 was found by both RT-PCR, micro-array analyses, and Western blot.

Thus, the specification shows the effect of vaccination with DNA encoding mesothelin in a mouse model of a peritoneal tumor which expresses mesothelin and MHC-1. The effect is shown by increased survival.

Induction of mesothelin-specific cytotoxic T lymphocytes is not specifically shown in this model. However, such induction is shown in another system taught in the specification. The specification teaches induction of a mesothelin-specific CD8⁺ T-cell response in vaccinated humans.

Fourteen humans were immunized with a whole cell pancreatic tumor vaccine which highly expresses mesothelin. Three of the patients developed a delayed type hypersensitivity reaction to autologous tumor cells (patients 8, 13, and 14). These same three patients (and none of the non-DTH responders) had extended disease-free survival far in excess of the expectation. See Table 2 at page 33. See declaration at paragraph 7 for continued follow-up on these long-term survivors. CD8⁺ T-cells were detected in patient 13 that responded to the two HLA-A3 binding mesothelin peptides. See Fig. 2A. Similar results were observed for patients 8 and 14. Page 36, [101]. “[E]ach of the three DTH responders demonstrated a past-vaccination induction in T-cell response to every mesothelin peptide that matched their respective HLA type, whereas only one of eleven DTH non-responders had an increased post-vaccination mesothelin-specific T-cell response and only to a single peptide.” *Id.* See also declaration at paragraph 9.

These data imply that mesothelin-specific T-cell responses are responsible for the increased survival observed in mesothelin-encoding DNA-vaccinated mice. Further experimentation demonstrated that T-cell lines derived from DTH-responding patients were capable of lysing mesothelin-expressing cells. Thus, the T-cells that are induced by mesothelin vaccination are cytolytic. See declaration at paragraph 10. See Thomas et al. (2004) at Figure 5.

Further data in another model system are described in the declaration in paragraphs 20-27. These demonstrate the use of *Listeria*-based mesothelin-encoding vaccines in a different mouse model. Both an antitumor and a CTL effect were observed in this system as well.

B. Pancreatic cancer is so malignant that treatment of it is unpredictable

The claims are directed to a method of inducing a T-cell response to a tumor which overexpresses mesothelin, resulting in a T-cell response to mesothelin. The data provided in both the specification and in the accompanying declaration provide evidence of efficacy associated with the induced T-cell response. As stated in the accompanying declaration of Dr. Jaffee, the original three DTH responders in the Phase I clinical study have now survived for over eight years. See paragraph 7. Moreover, the Phase II clinical study also demonstrates mesothelin-specific immune responses correlated with prolonged, progression-free survival. See paragraph 12. In addition, one and two year data indicate 88% and 76% survival. See paragraph 13.

These data, in combination with the mouse survival data shown in Figure 11 of the application indicate that the mesothelin-encoding DNA immunizations of the present invention will improve the life expectancy of pancreatic cancer patients. These hard data rebut any abstract notion that the claimed invention may not work due to the refractoriness of the disease.

C. Even if animal model data existed, their applicability to humans is unpredictable

The present invention, as described in the specification, is supported by both animal and human studies which are concordant. Both animal and human studies demonstrate a high degree of protection when a mesothelin-encoding DNA is used to immunize. The human data show induction of CD8⁺ T-cells which are specific for mesothelin by the immunization. The T-cell response correlated with long term survival. The animal data, too, shows long term survival. Thus, the data in animal models and humans support each other and are consistent with a positive response in the clinical setting.

The weight of the evidence provided in the specification and in the enclosed declaration of Dr. E. Jaffee, clearly demonstrates enablement of the claimed invention. Withdrawal of this rejection is respectfully requested.

Interview

The applicants are very grateful to the examiners for meeting with the inventor on March 14, 2007. The substance of the interview is reflected in the Patent Office Interview Summary and the Declaration of Dr. E. Jaffee.

Respectfully submitted,
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